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22428 7590 02/20/2009 FOLEY AND LARDNER LLP SUITE 500 3000 K STREET NW WASHINGTON, DC 20007				
EXAMINER				
SCHNITZER, RICHARD A				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

09/972,245

**Applicant(s)**

ROBERTS ET AL.

**Examiner**

Richard Schnizer

**Art Unit**

1635

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-42 and 44 is/are pending in the application.
- 4a) Of the above claim(s) 14-16 and 23-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13, 17-22, 41, 42 and 44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-884)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_
- Paper No(s)/Mail Date 8/22/08

### **DETAILED ACTION**

An amendment was received and entered on 12/4/08.

Claims 43, 45, and 46 were canceled.

Applicant has listed claims 23-40 as withdrawn. However, these claims were canceled in response to the Notice of Allowance (issued 4/18/08) that was withdrawn on 5/28/08. The Examiner is unaware of any mechanism whereby, once canceled, claims may be reinstated, except as newly numbered claims. Applicant is required to renumber claims 23-40 in accordance with 37 CFR 1.126, e.g. as claims 47-64.

Claims 1-22, 23-40 (47-64), 41, 42, and 44 are pending.

Claims 14-16 and 23-40 (47-64) stand withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/10/03.

Claims 1-13, 17-22, 41, 42, and 44 are under consideration.

### ***Rejections Withdrawn***

Applicant's amendments limiting the biological activity to the group consisting of an enzyme catalyzing a reaction, a molecule binding a receptor, mediating a receptor mediated response, antagonizing or blocking a receptor mediated response, induction of apoptosis, and release or reuptake of a neurotransmitter or hormone, overcame the rejections under 35 USC 102 over Wang (1993) and Tsutsumi (2000).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 17-22, 41, 42, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13, 17-22, 41, 42, and 44 are indefinite because it is not clear in independent claims 1, 42, and 44 that there is appropriate antecedent basis for "said immunocompetent subject", recited in claim 1 at page 3, line 3 of the amendment, in claim 42 at page 8, item (f) of the amendment, and in claim 44 at page 10, line 1 of the amendment. In each claim there are two possible antecedents for "said immunocompetent subject", as each claim recites "an immunocompetent subject" twice independently. See items (a) and (c) in claim 1, and items (b) and (d), in claims 42 and 44. It is unclear if these two recitations refer to the same immunocompetent subject or to different immunocompetent subjects. Accordingly, it is unclear if there is appropriate antecedent basis for "said immunocompetent subject" in the rejected claims.

Claims 1-13, 17-22, 41, 42, and 44 are also indefinite in their recitation of "mediating a receptor-mediated response such as ion/influx or generation of second messengers". The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 are rejected under 35 USC 103(a) as being unpatentable over the combination of Boos et al (Eur. J. Cancer 32A(9) : 1544-1550, 1996), Kawashima et al (Leukemia Res. 15(6): 525-530, 1991), Ettinger et al (Cancer 75: 1176-1181, 1995), Saito et al (Leukemia (1997 Apr) Vol. 11 Suppl. 3, pp. 408-9), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Boos studied the effects of using unmodified asparaginase from different sources, (*E. coli* or *Erwinia*) in the treatment of acute lymphoblastic leukemia because it was known that different asparaginase preparations had pharmacokinetic differences associated with increasing reports of hemorrhagic and thrombotic events. Boos stated that the pharmacologic aim of asparaginase treatment is the maximum reduction of asparagine concentration in patient's blood (page 1544, right column, lines 1-4), and made asparaginase activity the primary parameter for monitoring the effect of the drug on patients (page 1545, left column, lines 13-19). Patients were administered multiple doses of either of two *E. coli* asparaginase preparations, or of an *Erwinia* preparation, and asparaginase activity was assayed both before and after each administration. Boos established that the different preparations were not interchangeable, and found that each of the preparations provided different levels of activity after administration. See

abstract and Figs. 1-4. Thus Boos provided a template and motivation for comparing the effects and activities of different preparations of asparaginase *in vivo*.

Kawashima reported on the treatment of patients with hematological malignancies with 2, 4 - bis(*o*-methoxypolyethylene glycol)-6-chloro-S-triazine-conjugated L-asparaginase (PEG<sub>2</sub>-ASP). One patient, suffering non-Hodgkin's lymphoma, received treatment with unmodified L-asparaginase and suffered severe nausea, vomiting and loss of appetite. The patient went into remission, but later relapsed and was then treated with weekly or twice weekly intravenous infusion of PEG<sub>2</sub>-ASP, leading to complete remission within 2 months. The patient remained in complete remission for over one year with weekly infusions of PEG<sub>2</sub>-ASP. During this period blood asparagine was assayed but was not detectable. Serum levels of asparaginase activity were measured throughout the course of treatment, before and after multiple administrations of PEG<sub>2</sub>-ASP. See Fig. 1 on page 527 and Figs 2 and 3 on page 528. So, Kawashima taught a method of determining enzyme activity of PEG<sub>2</sub>-ASP in serum derived from blood samples before, after, and between, multiple administrations of the drug. Determination of the asparaginase activity in serum is considered to be an assay of the asparaginase activity in the blood sample.

Ettinger reported the results of a multi-center study of monomethoxypolyethylene glycol succinimidyl)74-L-asparaginase (Oncaspar or PEG-L-asparaginase). Patients suffering from acute lymphoblastic leukemia, who had previously been treated with unmodified L-asparaginase, received PEG-L-asparaginase at days 1 and 14 of treatment. Two thirds of evaluable patients achieved complete remission. See Fig. 1

on page 1177, and page 177, column 2, under "Clinical Laboratory Evaluation", and "Response Criteria". See also page 1178, column 1, last two paragraphs.

Saito studied the antitumor activity of L-asparaginase modified with a comb-shaped copolymer of polyethylene glycol and maleic anhydride (PM-asparaginase). Mice were inoculated intraperitoneally with murine lymphoma cells, and then received unmodified L-asparaginase or PM-asparaginase. Five out of six mice treated with PM-asparaginase were alive at day 60 and were free of tumors. PM-asparaginase had increased antitumor activity relative to unmodified asparaginase. See paragraph bridging pages 408 and 409.

Francis taught that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be affected by the way in which the protein drug is PEGylated. See abstract, and pages 2-4. Francis also taught that PEGylation of protein drugs can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a PEGylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

So, the prior art taught that the type and extent of PEGylation of therapeutic proteins could affect their activity and immunogenicity, such that it would be obvious to optimize these variables (see Francis above), and that PEGylation can also affect the bioavailability of the protein (see Ettinger at e.g. page 1176, column 2, second full paragraph of introduction). The cited prior art also taught three different forms of L-asparaginase (Kawashima, Ettinger, and Saito, respectively), each modified differently with a polyethylene glycol or a polyethylene glycol derivative, as well as a template for comparing different preparations of asparaginase (Boos). Given that all three forms of L-asparaginase had anticancer activity, and that it was known that differently modified enzymes often had different pharmacokinetic characteristics such as activity and half-life, it would have been obvious to one of ordinary skill in the art at the time of the invention to compare each of these modified asparaginases just as Boos had compared unmodified asparaginases of differing preparations. One would have been motivated to do so to determine which preparation was most efficacious. In so doing it would have been obvious to follow the protocols of Kawashima or Boos in which the catalytic activity of L-asparaginase in blood was determined throughout the course of treatment. One would have been motivated to do so because the presence of that catalytic activity is what provides a therapeutic effect (see Boos above). One would have been further motivated to perform such a comparative study in view of the teachings of Saito, who indicated that differentially modified asparaginases had different performance characteristics, i.e. Saito taught that PM-asparaginase reduced immunoreactivities at lower degrees of modification than PEG<sub>2</sub>-asparaginase. See Introduction on page 408.

One of ordinary skill also appreciates that different modifications may lead to differences in enzyme activity, immunoreactivity, and circulation time (see Francis and Ettinger, above). Accordingly, it would have been obvious to perform comparisons of activity in vivo, as taught by Boos.

Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph). Accordingly, it would be obvious to determine the relative catalytic activity of differently modified versions of L-asparaginase over the course of treatment, because there was reason to believe that some versions might be more or less active than others, and because it was routine in the art to make such measurements, as evidenced by Boos and Kawashima.

Claim 4 is rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Petersen et al (US 6,531,122, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also taught that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen taught that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, it was apparent from the teachings of Francis that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be differentially affected by the way in which the protein drug is PEGylated. See abstract.

Thus it would have been obvious to use different linkages in the process of optimizing these result-effective variables.

Thus the invention as a whole was prima facie obvious.

Claim 8, 11, and 20-22 are rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Abuchowski et al (Cancer Treat Rep 63(6): 1127-1132, 1979).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from *Pseudomonas*.

Abuchowski taught treatment of tumors in mice by administration of *Achromobacter* glutaminase asparaginase rendered nonimmunogenic by modification with polyethylene glycol. The resulting enzyme had greatly enhanced half life in blood and increased the survival of experimental mice inoculated with tumor cells when compared with unmodified glutaminase asparaginase. Abuchowski measured asparaginase activity in blood over time after a single injection of enzyme, and also measured mouse weight throughout the course of treatment in which mice were given PEGylated enzyme on alternate days. See Figures 3 and 4 on pages 1130 and 1131.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further study and compare differently modified *Achromobacter* glutaminase asparaginases in the process of optimizing PEGylation of this enzyme. One would have been motivated to do so because it was clear to those of ordinary skill in the art at the time of the invention that the amount and type of PEGylation was a result effective variable that influenced the activity of the enzyme as well as its serum half life and immunogenicity, as taught by Francis. In doing so it would have been obvious to determine the activity of the differently modified drugs by assay of catalytic activity as taught by Boos, Kawashima, and Abuchowski. In comparing the performance of two differently modified enzymes over the course of treatment, one of ordinary skill would practice all of the claimed method steps, such that the invention as claimed would have been obvious.

Claim 19 is obvious in view of the Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Bollin et al (US 4,678,812, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lyophilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

### ***Response to Arguments***

Applicant's arguments filed 12/4/08 have been fully considered as they might apply to the new ground of rejection set forth above but they are not persuasive.

Applicant addresses the obviousness rejections at pages 13-16 of the response.

Applicant's arguments at pages 13 and 14 are essentially directed to portions of the rejections of 6/6/08 that indicated that determining the levels of various types of blood cells in patients undergoing asparaginase treatment served as an indirect measure of asparaginase activity. Applicant argues that these are not measures of biological activity. The amendment of 12/4/08 is considered to render that issue moot by requiring assay of a blood sample for biological activity, wherein the biological activity is an enzyme catalyzing a reaction, among other recited activities. For the embodiment of an enzyme catalyzing a reaction, the claim as amended is interpreted as requiring the assay of a process that is occurring, or can occur, in the isolated sample.

The measurement of the amounts of particular blood cells that are affected by the activity of asparaginase is not considered to meet the limitations of the claims as amended. However, both Kawashima and Boos taught the measurement of blood asparaginase activity throughout the course of treatment with asparaginase, and the cited art is considered to render obvious the claims as amended.

At pages 14 and 16, Applicant implies that the Examiner attempts to recreate the invention through a hindsight reconstruction. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See MPEP 2145 (IX)(A). Applicant did not pointed to any claim limitation that was met by using knowledge gleaned only from the applicant's disclosure, and not the prior art. Instead, Applicant argued that the Examiner cherry-picked various steps used to determine the modification conditions of a therapeutic agent to prevent host-mediated inactivation from among countless combinations. This is unpersuasive. The Examiner provided an example of researchers (Boos et al) comparing different asparaginase preparations known to have different pharmacological characteristics, in which the researchers measured asparaginase activities throughout the course of treatment. The Examiner provided examples of several differently modified asparaginases (Kawashima, Ettinger, and Saito), and also showed that it was known that the type and extent of modification can affect enzyme activity and other

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performance characteristics (Francis, Saito). So, one of ordinary skill would reasonably have expected differently modified asparaginases to have different pharmacokinetic parameters, and would have been motivated to compare them as taught by Boos. It would also have been obvious to measure other outcomes, such as blood asparagine levels, and the amounts of various blood cells, but this does not mean that it would not have been obvious to measure enzyme activity throughout the course of treatment, as taught by Boos and Kawashima. Note that Kawashima performed all of these assays (blood asparagine, blood asparaginase, and levels of various blood cells). Accordingly, the Examiner has not cherry-picked from among the teachings of the art. Instead the teachings of the art have been objectively considered and a determination has been made that it would have been obvious to one of ordinary skill in the art at the time of the invention to execute the claimed method steps. Applicant is reminded that the reason for combining the references need not be the same as that which motivated Applicant to make their invention (MPEP 2144 (IV)).

Applicant asserts that the Examiner has not shown an apparent reason to combine the prior art elements in the fashion claimed with an expectation of success. This is incorrect. The Examiner stated that one of ordinary skill would have been motivated to compare the known modified asparaginases to determine which had the best performance characteristics, and that one would have been motivated to assay asparaginase activity because one of ordinary skill appreciates that the presence of that catalytic activity is what provides a therapeutic effect.

To support the position that the references have been combined without an

adequate expectation of success, Applicant attempts to form an analogy with the situation in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), in which the prior art disclosed a broad selection of compounds, any one of which could have been selected for further investigation which might have led to development of a claimed drug, and the court found that the claimed drug was not obvious over the cited art. Applicant's reliance on Takeda is misplaced because the situation is non-analogous. The issue in Takeda was obviousness of a compound and compositions containing the compound, whereas the instant claims are drawn to methods. As a result, the nature of the analogy is not completely clear. It is the Examiner's understanding that Applicant is drawing a parallel between the claimed compound in Takeda and the step of measuring biological activity in the instant claims. In Takeda the cited prior art disclosed lead compounds from which, the court decided, it would not have been obvious to arrive at the claimed compound. In contrast, the instantly cited art discloses the precise means of measuring biological activity recited in the instant claims, i.e. Kawashima and Boos each measure activity of a modified enzyme after repeated administrations of the enzyme. What is missing from Kawashima and Boos is a comparison of two differently modified enzymes. However, the prior art disclosed several differently modified enzymes (Kawashima, Ettinger, and Saito), and motivation to compare them is provided by the recognition that activity can be affected differently by different modifications (Francis, Saito).

Applicant appears to argue that because the art taught that many outcomes could be measured in comparing two differently modified enzymes, that it would not

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have been obvious to choose the enzyme activity assay of Kawashima (or Boos). In other words it would not have been obvious to select enzyme activity as an assay when other outcomes such as blood asparagine, tumor size, or the amounts of various types of blood cells could be measured as outcomes. This is unpersuasive because, in fact, Kawashima used all of these assays. So, in essence, the analogs of all the lead compounds were selected by Kawashima for "further investigation". Applicant's statement at page 15 that "nothing in the cited material would have guided an artisan contemplating a method of determining the modification conditions of a therapeutic agent to prevent host-mediated inactivation to a method specifically measuring biological activity as claimed" is incorrect. The teachings of Kawashima would have led one of ordinary skill to assay all of the variables assayed by Kawashima when analyzing the usefulness of one or more variants of asparaginase, including asparaginase activity. Furthermore, the Boos reference provides motivation to measure asparaginase activity specifically, because it is "primary parameter" of drug monitoring in that study (see page 1545, left column , lines 17-19).

Applicant argues at page 15 that the cited material presents myriad timing options for conducting measurements, and that "nothing in the cited material hints of a method for determining the modification conditions of a therapeutic agent to prevent host mediated inactivation where a therapeutic agent is modified in two different ways and the biological activities of the two modified agents are compared *after each modified agent has been administered at least twice*" (emphasis in original). Applicant disqualifies the teachings of Kawashima and Ettinger because they were not optimizing

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the modification level of a therapeutic agent, but instead were simply monitoring the effects of administered drugs over the course of treatment. This is unpersuasive. MPEP 2144 (IV) indicates that the reason for combining the references need not be the same as that which motivated Applicant to make their invention. Thus the fact that Kawashima was simply monitoring the effects of the drug over the course of treatment is immaterial. The teachings of Kawashima and Boos would have suggested to one of skill in the art to measure blood asparaginase activity over the course of treatment when testing a modified asparaginase, or when comparing different asparaginases. It would have been obvious to compare differently modified asparaginases because several were known to exist, and because it was well known that different modifications could lead to different activities and efficacies.

For these reasons the rejections are maintained.

The Declaration under 37 CFR 1.132 of Natarajan Sethuraman, filed 12/4/08 has been fully considered. The Declaration is directed to the issue of what one of skill in the art would consider to be suitable as an assay for measuring the enzymatic activity of a modified asparaginase. This issue is considered to be moot in view of the claims as amended, and the basis of the rejection as stated above, which depends on the use of a direct assay of blood asparaginase activity as disclosed by Kawashima and Boos.

***Prior Art Made of Record But Not Relied Upon***

Chua et al (Ann. Int. Med. 109 : 114-117, 1988), studied the use of PEG-modified uricase to treat hyperuricemia. The patient was administered 4 doses of PEG-modified

uricase, and plasma uricase activity was measured several times after each administration, see Fig. 1.

Muller et al (Brit. J. Haem. 110 : 379-384, 2000) studied blood asparaginase activity in patients on each of several days after a single administration of pegylated asparaginase. See abstract, Table I, and Fig. 1.

### ***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-

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272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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/Richard Schnizer/  
Primary Examiner, Art Unit 1635